REMARKS

Claims 1-54 are pending in the present application. By virtue of this response, claims 1, 13, and 26 have been amended, and claims 3, 15, 28, 39-50 and 54 have been cancelled. Claims 1, 13, and 26 have been amended to incorporate the limitations in claims 3, 15, and 28. Accordingly, no new matter has been added.

With respect to all claim amendments, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in a future continuation and/or divisional application.

Information Disclosure Statement

The Examiner states that the IDS papers submitted August 30, 2004 and September 27, 2005 have previously been considered and entered of record, and the IDS paper submitted May 3, 2006 is signed and initialed. Applicants note that reference 37 in the IDS paper submitted September 27, 2005 and references 18-21, 23, and 24 in the IDS paper submitted May 1, 2006 have not been initialed by the Examiner. Accordingly, Applicants respectfully request the Examiner initial these references.

Maintained Rejections

Claim Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 39-50 and 54 stand rejected under 35 U.S.C. § 112, first paragraph. The Examiner alleges that the specification, while being enabling for a method of reducing pathology associated with Alzheimer's disease in transgenic mice, does not reasonably provide enablement for a method of delaying development of a symptom associated with Alzheimer's disease as broadly claimed.

Applicants respectfully disagree with the Examiner and reiterate that the application teaches how to make and use the claimed invention. However, in the interest of expediting prosecution, claims 39-50 and 54 have been cancelled. Accordingly, this rejection becomes moot. Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, be withdrawn.

Obviousness-Type Double Patenting

A. Claims 1-4, 6, 10-16, 18, 22-24, 26-29, 31, 35-37, 39-42, 44, and 48-50 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 7-17, 19, 28, 31-40, and 42 of copending Application No. 11/194,989. Claims 51-54 are similarly rejected as being unpatentable over claims 2 and 28 of Application No. 11/194,989.

Applicants respectfully request that this rejection be held in abeyance until the Office has made a determination of allowable claims in the present application or in copending App. Ser. No. 11/194,989, at which time Applicants will address this issue.

B. Claims 1-4, 6, 10-16, 18, 22-24, 26-29, 31, 35-37, 39-42, 44, and 48-50 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 6-15, 17, 26, 29-38, and 40 of copending Application No. 11/195,207. Claims 51-54 are similarly rejected as being unpatentable over claims 2 and 28 of Application No. 11/195,207.

Applicants respectfully request that this rejection be held in abeyance until the Office has made a determination of allowable claims in the present application or in copending App. Ser. No. 11/195,207, at which time Applicants will address this issue.

Claim Rejections Under 35 U.S.C. § 102

A. Claims 1, 2, 4, 6, 8-10, 13, 14, 16, 18, 20-22, 25-27, 29, 31, 33-35, 38-40, 42, 44, and 46-48 stand rejected under 35 U.S.C. 102(b) as allegedly being unpatentable over Bard *et al.* (*Nat. Med.*, August 2000; 6(8): 916-919, cited on Applicant's IDS received 8/30/04).

Applicants note that claims 1, 13, and 26 have been amended to recite the limitations in claims 3, 15, and 28, and claims 3, 15, and 28 are not rejected by the Examiner on this basis. The claims as amended are directed to the use of an antibody that binds preferentially to amino acids 28-40 of $A\beta_{1-40}$ peptide and does not show significant cross-reactivity with $A\beta_{1-42}$ and $A\beta_{1-43}$ peptide for treating Alzheimer's disease, suppressing the formation of amyloid plaques, or reducing amyloid plaque in a subject.

Applicants note that claims 39, 40, 42, 44, and 46-48 have been cancelled. Thus, rejection of these claims becomes moot.

To anticipate a claim, a prior art reference must teach each and every element set forth in the claim. MPEP §2131. Applicants respectfully submit that Bard *et al.* do not teach or suggest the claimed invention. As pointed out by the Examiner, Bard et al. evaluates antibodies for therapeutic use in the treatment of Alzheimer's disease using a transgenic mouse model (PDAPP mice) of Alzheimer's disease. One of the antibodies evaluated by Bard et al. is the monoclonal antibody 21F12, which has a reported epitope of $A\beta_{33-42}$. Although amino acids 33-40 are within this epitope, this does not necessarily suggest that antibody 21F12 preferentially binds to amino acids 28-40 of $A\beta_{1-40}$ as discussed in the previous response. For example, if binding of the antibody depends on the last two amino acids on the C-terminus of $A\beta_{\underline{33-42}}$, this antibody will likely not bind to $A\beta_{\underline{1-40}}$ because those two amino acids are not present on the C-terminus of $A\beta_{1-40}$. In addition, Applicants submit a paper by Johnson-Wood et al. (a co-author of Bard et al.; *Proc. Natl. Acad. Sci.* U.S.A. 94: 1550-1555, 1997) for Examiner's consideration. In this paper, the specificities of antibody 21F12 to $A\beta_{\underline{1-40}}$ and $A\beta_{\underline{1-42}}$ were tested; and antibody 21F12 were demonstrated to show negligible crossreactivity (<0.4%) with $A\beta_{\underline{1-40}}$ in either ELISA or competitive radioimmunoassay (RIA). See, page 1551, right col., lines 19-29. As defined in the specification of the present application, the term "preferentially binds" means an antibody binds to one substance with greater affinity, avidity, more readily, and/or with greater duration than it binds to other substances. See paragraph [0055]. Although under this definition, an antibody that preferentially binds to a first target may also preferentially bind to another target, "negligible crossreactivity" is not within the definition of "preferentially binds". Since antibody 21F12 does not preferentially bind to $A\beta_{1-40}$, this antibody does not meet the limitation recited in the original claims.

Applicants disagree with the Examiner's conclusion that the claims are anticipated by Bard et al. because "the Bard et al. reference explicitly suggests the step of administering an effective amount of a pharmaceutical composition comprising a monoclonal anti-Aβ antibody to a subject for the treatment of Alzheimer disease, wherein the disclosed antibody meets several of the claim limitations" (emphasis added). See Office Action, page 8. Applicants respectfully note that the test for anticipation by a prior art reference is whether the prior art reference teaches each and every limitation in the claims, and meeting several of the claim limitations is not enough for a prior art reference to be anticipating.

Applicants also note that soluble Aβ includes all forms of Aβ, such as $A\beta_{1-40}$, $A\beta_{1-42}$, and $A\beta_{1-43}$. Table 1 in Bard et al. does not specify which soluble Aβ that the affinity was measured with. Since there are various forms of soluble Aβ, one skilled in the art could not know to which soluble Aβ the affinity is referring by reading the paper. In addition, since antibody 21F12 only shows negligible crossreactivity with $A\beta_{1-40}$ as disclosed in Johnson-Wood et al., the affinity indicated in Table 1 could not be interpreted to be the affinity of antibody 21F12 for $A\beta_{1-40}$. Accordingly, Bard et al. do not disclose that the affinity of 21F12 to $A\beta_{1-40}$ is 80 nM. Thus, the Examiner has not shown that antibody 21F12 meets the affinity limitations recited in the dependent claims.

In view of the above, Applicants respectfully submit that the Examiner has not shown that antibody 21F12 meets the limitation of preferentially binding to amino acids 28-40 of $A\beta_{1-40}$ as recited in the claims.

Applicants respectfully submit that Bard et al. do not anticipate the original claims of the instant application by the principle of inherency. Although a reference may still anticipate if a particular element not expressly disclosed in the reference is inherent in its disclosure, "[t]o establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.'" *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (citing *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991)). The Court further states that "[i]nherency, however, may not be established by probabilities or possibilities", and "[t]he mere fact that a certain thing may result from a given set of circumstances is not sufficient". *Id.* (citing *Continental Can Co.*, at 1269; quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)). In the present application, the Examiner has not established that antibody 21F12 necessarily has the characteristics of preferentially binding to A$\beta_{1\text{-}40}$ as recited in the claims. Instead, the Examiner relied on the mere possibility that antibody 21F12 has the characteristics recited in the claims. In addition, Bard et al. teach that this antibody is ineffective for removing plaques in the animal model for Alzheimer's disease. Accordingly, One skilled in the art would not reasonably expect that this antibody could be used for treating Alzheimer's disease, and performs the same as the claimed invention. For the above stated reasons, the Examiner has not established that Bard et al. anticipate the claimed invention by inherency.

In the interest of expediting prosecution, claims 1, 13 and 26 have been amended to recite that the anti-Aβ antibody does not show significant cross-reactivity with A$\beta_{1\text{-}42}$ and A$\beta_{1\text{-}43}$ peptide. None of the anti-Aβ antibodies disclosed in Bard et al. meets this limitation since the anti-Aβ antibodies disclosed in Bard et al. specifically bind to A$\beta_{1\text{-}42}$. Thus, Bard *et al.* fail to disclose a method of administering an antibody that binds preferentially to amino acids 28-40 of A$\beta_{1\text{-}40}$ peptide and does not show significant cross-reactivity with A$\beta_{1\text{-}42}$ and A$\beta_{1\text{-}43}$ for treating Alzheimer's disease, suppressing formation of amyloid plaques, or reducing amyloid plaque, as recited by the present claims as amended. Accordingly, Bard et al. do not anticipate the claims as amended.

In view of the above, Bard *et al.* do not anticipate claims 1, 2, 4, 6, 8-10, 13, 14, 16, 18, 20-22, 25-27, 29, 31, 33-35, and 38 as amended. Withdrawal of this rejection is therefore respectfully requested.

B. Claims 1, 2, 8-14, 20-27, 33-40, 46-50, and 51-54 stand rejected under 35 U.S.C. 102(e) as being anticipated by Schenk (U.S. Patent No. 6,787,523). The Examiner states that Schenk teaches the use of an anti-Aβ antibody in the treatment of Alzheimer's disease. The Examiner further states that the antibody 21F12 meets all the recited antibody claim limitations.

Applicants note that claims 1, 13, and 26 have been amended to recite the limitations in claims 3, 15, and 28, and claims 3, 15, and 28 are not rejected by the Examiner. The claims as amended are directed to the use of an antibody that binds preferentially to amino acids 28-40 of $A\beta_{1-40}$ peptide and does not show significant cross-reactivity with $A\beta_{1-42}$ and $A\beta_{1-43}$ peptide for treating Alzheimer's disease, suppressing the formation of amyloid plaques, reducing amyloid plaques, or delaying the development of a symptom associated with Alzheimer's disease in a subject having Alzheimer's disease.

Applicants further note that claims 39, 40, 46-50, and 54 have been cancelled. Thus, rejection of these claims becomes moot.

As discussed above, to anticipate a claim, a prior art reference must teach each and every element set forth in the claim. MPEP §2131. Applicants respectfully submit that the disclosures in Schenk do not teach or suggest the claimed invention. Schenk provides a prophetic example for administering anti-Aβ antibodies, such as 21F12, to PDAPP mice over a 4 month period and performing post mortem analysis of Aβ levels and toxicology. As discussed above, antibody 21F12 does not meet the limitation of preferentially binding to amino acids 28-40 of $A\beta_{1-40}$.

In addition, the claims as amended recite administering antibodies that do not show significant cross-reactivity with $A\beta_{1-42}$ and $A\beta_{1-43}$ peptide. Antibody 21F12 does not meet this limitation because this antibody specifically binds to $A\beta_{1-42}$. Thus, this antibody is excluded from the antibodies recited in the claims as amended. Since Schenk fails to disclose a method of administering an antibody that binds preferentially to amino acids 28-40 of $A\beta_{1-40}$ peptide and does not show significant cross-reactivity with $A\beta_{1-42}$ and $A\beta_{1-43}$ for treating Alzheimer's disease, suppressing formation of amyloid plaques, or reducing amyloid plaque, as recited by the present claims as amended, this reference does not anticipate the claimed invention.

Accordingly, Schenk does not anticipate claims 1, 2, 8-14, 20-27, 33-38, and 51-53 as amended. Withdrawal of this rejection is therefore respectfully requested.

Claim Rejections Under 35 U.S.C. § 103

Claims 1, 2, 4-14, 16-27, 29-40, and 42-54 stand rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Bard *et al.* (*Nat. Med.*, August 2000, 6(8): 916-919) in view of Zietlin *et al.* (*Microbes and Infections*, 2000, 2: 701-708). The Examiner states that Bard *et al.* teach the use anti-Aβ antibodies to reduce pathology in PDAPP transgenic mice as set forth *supra*; however, Bard *et al.* do not teach lower antibodies affinities for this monoclonal antibody (such as 1 nM or less) or humanized or human antibodies. The Examiner further states that Zeitlin *et al.* teach or suggest that monoclonal antibodies, antibodies with improved affinities, humanized antibodies, and fully human antibodies may achieve a better clinical benefit. It is the Examiner's position that it would have been obvious to the persons of ordinary skill in the art at the time the invention was made to arrive at the claimed invention by combining the methods of reducing amyloid burden in a Alzheimer's disease model using the monoclonal antibody 21F12 as taught by Bard *et al.* with selecting for high affinity monoclonal, humanized, or human monoclonal antibodies as taught by Zeitlin *et al.* to create high affinity, humanized, or human anti-Aβ antibodies for the treatment of Alzheimer's disease. The Examiner further alleges that one of skill in the art would have been motivated to make these modifications and would have an expectation of success in treating Alzheimer's disease because Bard *et al.* teach that it would be expected to work.

Applicants note that claims 1, 13, and 26 have been amended to recite the limitations in claims 3, 15, and 28, and claims 3, 15, and 28 are not rejected by the Examiner on this basis. The claims as amended are directed to the use of an antibody that binds preferentially to amino acids 28-40 of $A\beta_{1-40}$ peptide and does not show significant cross-reactivity with $A\beta_{1-42}$ and $A\beta_{1-43}$ peptide for treating Alzheimer's disease, suppressing the formation of amyloid plaques, or reducing amyloid plaques.

Applicants further note that claims 39, 40, 42-50, and 54 have been cancelled. Thus, rejection of these claims becomes moot.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art references (alone or in combination) must teach or suggest all the claim limitations. These requirements are summarized in the MPEP (MPEP §2143, and §2143.01 to §2143.03), and are based on well-settled case law: *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); and *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

Applicants submit that the cited references, even if combined, do not teach or suggest all of the claimed limitations. As discussed in the above section, Bard *et al.* do not teach or suggest methods for treating Alzheimer's disease, suppressing formation of amyloid plaques, reducing amyloid plaques, or delaying development of a symptom associated with Alzheimer's disease in a subject having Alzheimer's disease by administering an antibody that binds preferentially to amino acids 28-40 of $A\beta_{1-40}$ peptide and does not show significant cross-reactivity with $A\beta_{1-42}$ and $A\beta_{1-43}$ peptide, as required by the present claims as amended. The above discussion applies equally here. Zeitlin *et al.* do not cure this deficiency of Bard *et al.* Zeitlin *et al.* do not teach or suggest using an anti-Aβ antibody for treating Alzheimer's disease. Instead, Zeitlin *et al.* describe attributes of a variety of antibodies that are potentially useful in therapeutic indications, focusing on infectious disease.

In response to the Examiner's assertion that the Applicants' prior arguments only addressed each reference individually rather than addressing the combination of references, Applicants note that even if one were motivated to combine the teachings of Bard *et al.* and Zeitlin *et al.*, this combination does not teach or suggest all of the claim limitations. In particular, this combination of references does not teach or suggest the claimed methods of using an antibody that binds preferentially to amino acids 28-40 of $A\beta_{1-40}$ peptide and does not show significant cross-reactivity with $A\beta_{1-42}$ and $A\beta_{1-43}$ peptide for treating Alzheimer's disease, suppressing formation of amyloid plaques, or reducing amyloid plaque. Thus, the obviousness rejection may be properly withdrawn on this ground.

Applicants also submit that one skilled in the art would not have been motivated to combine the teachings of Bard *et al.* about antibodies to $A\beta_{33-42}$ that do not have *in vivo* efficacy in clearing plaques with the teachings of Zeitlin *et al.* about high affinity monoclonal, humanized, or human monoclonal antibodies. In particular, a presumption of obviousness "is not created when the reference compound is so lacking in any utility that there is no motivation to make close relatives." *In re Dillon*, 919 F.2d 688, 697 (Fed. Cir. 1990) (citing *In re Stemniski,* 444 F.2d 581 (C.C.P.A. 1971)). "*Albrecht* followed this line of thinking when it held that the prior art compound so irritated the skin that it could not be regarded as useful and therefore did not create a motivation to make related compounds." *Id.* (citing *In re Albrecht,* 514 F.2d 1389, 1392 & 1395-96 (C.C.P.A. 1975)).

Rather than motivating a skilled artisan to arrive at the claimed invention, Bard *et al.* teach away from the concept of using antibodies directed to C-terminal amino acid residues of an Aβ peptide to clear amyloid plaques. Bard *et al.* state that in a comparison of six different antibodies tested, antibodies 10D5, 3D6 and pabAβ1-42 were all active in the *ex vivo* assay and demonstrated efficacy *in vivo*; in contrast, 16C11, 21F12 and the control antibody TM2a were inactive in both assays. *See*, page 917, right col., line 16 to page 918, left col., line 1. Antibodies 3D6 and 10D5 have reported to bind to amino acid residues 1-5 and 3-6, respectively. *See* WO 00/72880, page 97, Table 16. Antibody pab$A\beta_{1-42}$ is a polyclonal antibody obtained from mice immunized with $A\beta_{1-42}$. *See* Bard *et al.*, page 916, left col., lines 33-35. Since Bard *et al.* teach that antibodies that bind to $A\beta_{33-42}$ do not have *in vivo* efficacy in clearing plaques, a person of ordinary skill would be discouraged from developing other antibodies directed to C-terminal residues of an Aβ peptide for therapeutic use in Alzheimer's disease. Thus, one skilled in the art would not have been motivated to make and use these antibodies.

Additionally, a *prima facie* case of obviousness has not been established because there would not have been a reasonable expectation of success. As discussed above, Bard *et al.* disclose that both antibody 21F12 and antibody 16C11, which bind to $A\beta_{33\text{-}42}$, lack *in vivo* efficacy in removing plaques in the animal model. Bard *et al.* provide no suggestion or basis for one skilled in the art to expect that antibodies having *in vivo* efficacy can be generated by improving the affinity of these antibodies, humanizing these antibodies, or making a human antibody to the same epitope. Zeitlin *et al.* teach some of the unique qualities of monoclonal antibodies in treating or preventing infectious diseases, which are quite different from Alzheimer's disease. Based on the above, it would not have been obvious for one of ordinary skill in the art to combine the teachings of these two references with a reasonable expectation of success in removing plaques and treating Alzheimer's disease using antibodies that bind to C-terminal amino acid residues of an Aβ peptide. Specifically, a skilled artisan would not have had a reasonable expectation of success that such antibodies would be useful in treating Alzheimer's disease, suppressing formation of amyloid plaques, reducing amyloid plaques, or delaying development of a symptom associated with Alzheimer's disease, as required by the present claims. On this ground, the obviousness rejection may be properly withdrawn.

In view of the above, the Examiner has not set forth a *prima facie* case for obviousness for claims 1, 2, 4-14, 16-27, and 29-38. Accordingly, Applicants respectfully request the rejection under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 514712001500. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: December 20, 2006

Respectfully submitted,

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